

Fodor says. For higher cell numbers and for whole-genome coverage, sequencing capacity would become a limiting factor. ■

## T-cell Therapy Targets Glioblastoma

A team of researchers successfully engineered T cells to express a chimeric antigen receptor (CAR) that targets a mutation associated with a particularly aggressive form of glioblastoma, laying the foundation for a phase I clinical trial.

In a preclinical study, researchers redirected humanized CAR T cells to bind to the EGFR variant III mutation (EGFRvIII), a common variant of EGFR in human tumors that occurs in about 30% of patients with glioblastoma and is associated with poorer prognosis. Investigators designed CAR T cells using humanized single-chain variable fragments (scFv) that showed specificity for EGFRvIII over wild-type EGFR. In mice, the EGFRvIII CAR T cells successfully controlled tumor growth, and deeper regression was observed when they were combined with temozolomide chemotherapy, a standard treatment for glioblastoma (*Sci Transl Med* 2015;7:275ra22).

“Studying genetically engineered T cells is a hot area because of the tremendous success there has been with leukemia,” says the study’s senior author Marcela Maus, MD, PhD, assistant professor of hematology/oncology at the University of Pennsylvania Abramson Cancer Center in Philadelphia. “This phase I trial will be the first time that we are trying this particular method of engineering T cells to target glioblastoma in humans.”

Although CAR T-cell therapy has shown promise for treating blood cancers, solid tumors have been more challenging because many targetable surface antigens on solid tumors are also expressed in normal cells. However, the authors noted that EGFRvIII might be an ideal CAR target because it is specific to malignant cells and plays a critical role in maintaining oncogenesis.

The researchers, including scientists from Novartis Institutes for BioMedical

Research, tested a panel of scFvs *in silico* and *in vitro* in order to determine the degree of specificity to EGFRvIII and cross specificity with wild-type EGFR. They then further tested the lead humanized CAR for safety in mouse models grafted with normal EGFR-expressing human skin.

The investigators also tested the lead humanized CAR for efficacy in three mouse models implanted with human glioblastoma cell lines, says Maus. The CAR T cells controlled or shrank most tumors whether the tumors were intracranial or under the skin. Administered intravenously, the engineered T cells controlled the tumor most effectively when given in combination with temozolomide.

The study is the basis for a new phase I trial, based at Penn and the University of California, San Francisco, that is currently enrolling up to 12 adults with EGFRvIII-positive glioblastoma who have either relapsed after standard therapy or have residual disease following surgery, says Maus. Investigators will remove patients’ own T cells and reprogram them to target EGFRvIII-expressing tumor cells when they are returned to the patients via intravenous injection. ■

## Improving PET Evaluation of Brain Tumors

To survive and proliferate, cancer cells undergo metabolic reprogramming and avidly consume various nutrients, including glucose. <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG), a glucose analog, is usually the radiolabeled tracer of choice when PET is used to evaluate tumors.

However, not all cancers can be clearly imaged with <sup>18</sup>F-FDG-based PET, including glioma, an aggressive form of brain cancer. “It’s difficult to distinguish these tumors, because normal brain cells also metabolize high amounts of glucose,” says Sriram Veneti, MD, PhD, a neuropathologist at the University of Michigan in Ann Arbor and first author of a recent study showing that <sup>18</sup>F-fluoroglutamine (<sup>18</sup>F-FGln), an analog of the amino acid glutamine, is a more specific PET tracer for glioma in mice and humans (*Sci Transl Med* 2015;7:274ra17).

Highly dependent on glutamine, many cancers synthesize it and import still more from extracellular sources. Hypothesizing that “this addiction could be leveraged to noninvasively assess brain tumors,” Veneti collaborated with colleagues at Memorial Sloan Kettering Cancer Center in New York, NY, and the University of Pennsylvania in Philadelphia to develop <sup>18</sup>F-FGln.

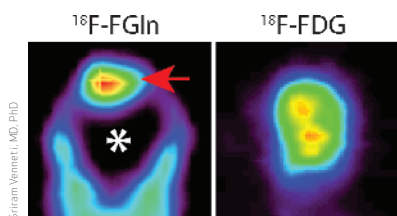
In several mouse models of glioma, the researchers found that the uptake of <sup>18</sup>F-FGln was significantly higher in tumors than in normal brain tissue. In contrast, the uptake of <sup>18</sup>F-FDG was equivalent in tumors and normal tissue. With <sup>18</sup>F-FGln, tumor-to-background ratios ranged from 4:1 to 6:1, enabling clear tumor delineation; this ratio was approximately 1:1 with <sup>18</sup>F-FDG. The researchers verified that the marked <sup>18</sup>F-FGln uptake seen in glioma was not influenced by neuroinflammation or a leaky blood-brain barrier.

Veneti’s team then compared <sup>18</sup>F-FGln with MRI in imaging glioma-bearing mice before and after treatment with chemotherapy and radiation. <sup>18</sup>F-FGln’s uptake dropped significantly after treatment; however, MRI scans before and after were not appreciably different.

Ralph DeBerardinis, MD, PhD, an associate professor at the University of Texas Southwestern Medical Center in Dallas, is encouraged that <sup>18</sup>F-FGln-based PET “reports therapy-induced metabolic changes in these mice long before tumor size changes” on MRI. “This is exactly what glucose-based PET monitors in many other cancers, but has been difficult to capture in gliomas,” he says.

Additionally, <sup>18</sup>F-FGln-based PET may help separate pseudoprogression—a treatment-related MRI pattern mimicking disease progression—from actual tumor recurrence, “a difficult distinction to make in the clinic,” Veneti adds.

Testing the agent in patients who had undergone surgery, Veneti and his colleagues saw avid uptake and retention of <sup>18</sup>F-FGln in three patients whose gliomas recurred, but not in three others whose tumors had not. Where <sup>18</sup>F-FDG outlined only part of the tumor in one patient, <sup>18</sup>F-FGln



Researchers used two different radiolabeled tracers to create PET images of a mouse's brain:  $^{18}\text{F}$ -FDG, which is traditionally used, and  $^{18}\text{F}$ -FGln.  $^{18}\text{F}$ -FGln (left) clearly shows the location of a glioma (red arrow) and normal brain tissue (white asterisk). Normal brain cannot be differentiated from tumor in the  $^{18}\text{F}$ -FDG image.

clearly delineated the same tumor in its entirety—which is important, Venneri notes, because gliomas are highly invasive.

“Hopefully, this agent performs as well outside the brain,” says Peter Choyke, MD, director of the NCI's molecular imaging program in Bethesda, MD. “It will be particularly interesting to see whether glutamine uptake in tumors leads to clinical responses for a new generation of drugs targeting glutamine transport and metabolism.” ■

## Parsing Pancreatic Cancer

In a recently reported study, whole-genome sequencing of 100 pancreatic ductal adenocarcinomas identified four tumor subtypes based on DNA structural variation, distinctions that may help guide treatment choices in the future (*Nature* 2015;518:495–501).

Current treatments for pancreatic cancer are often toxic and work in only a subset of patients. Matching treatments to patients who might benefit remains an urgent need, says study co-director Andrew V. Biankin, MD, PhD, of the University of Glasgow in Scotland and the Garvan Institute of Medical Research in Sydney, Australia.

In collaboration with the International Cancer Genome Consortium, the researchers performed deep whole-genome sequencing and copy number–variation analysis on tissue from early-stage tumors. The study extended previous exome sequencing analysis, and found both known

and new genes mutated at moderate or high frequency and many genes mutated at low frequency. More importantly, Biankin says, the whole-genome approach revealed structural aberrations that contribute significantly to the overall mutational burden in tumors, including the deletion, amplification, and rearrangement of large pieces of DNA.

Analysis of patterns of structural variation identified four distinct tumor types: stable, locally rearranged, scattered, and unstable. The stable group had the fewest DNA rearrangements, while the locally rearranged and scattered groups showed an intermediate level, clustered on one or two chromosomes or distributed among multiple chromosomes, respectively. The unstable group, accounting for 14% of tumors, showed the most frequent structural changes, with more than 200 per genome. Most of the tumors in this group had mutations in key maintenance and repair enzymes—BRCA1, BRCA2, or PALB2—or displayed a mutational signature of DNA repair deficiency.

Because DNA repair deficiency may impart sensitivity to DNA-damaging drugs, the researchers looked at outcomes for patients who had received platinum-based chemotherapy. Of eight patients in the study treated with platinum agents, four of the five with unstable genomes and/or a mutational signature of DNA repair deficiency responded to treatment. Three patients with other tumor subtypes did not respond.

“These are small numbers, so we have to be cautious, but this is a potential biomarker for us to take forward into clinical trials and start to test whether we can better select patients for specific treatment,” Biankin says.

That possibility excites Steven D. Leach, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who was not involved in the work. “For the first time in pancreatic cancer, we see genomic data that may have predictive value in terms of what therapies are likely to work for subsets of patients,” he says. ■

## NOTED

- **Eli Lilly and Company and Beijing, China's Innovent Biologics announced that they will collaborate** on the development and potential commercialization of at least three cancer treatments over the next decade. The collaboration will include Lilly's cMet monoclonal antibody (mAb) for possible treatment of non-small cell lung cancer and Innovent's mAb targeting CD-20 for possible treatment of hematologic malignancies.
- **Apple launched a mobile app to track quality of life of breast cancer survivors.** Data will be used to study why some survivors recover faster than others, why symptoms vary, and what can be done to improve problems such as fatigue, mood and cognitive changes, and sleep disturbances. The app is part of Apple's ResearchKit, which is designed to expand participation in research studies.
- At the Endocrine Society's 97th annual meeting in San Diego, CA, researchers presented results of a phase II trial of sunitinib (Sutent; Pfizer) showing that **19 of 24 patients with advanced-stage differentiated thyroid cancer experienced either significant tumor shrinkage or stable disease.** The median progression-free survival was 241 days. Sunitinib is approved for the treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors.
- **Bloomberg Philanthropies and the Bill & Melinda Gates Foundation launched the Anti-Tobacco Trade Litigation Fund** to help combat the tobacco industry's use of international trade agreements to threaten countries and prevent them from passing strong tobacco-control laws. The fund, established with \$4 million from the organizations, will help low- and middle-income countries draft and defend tobacco-control laws.
- **Two out of three people diagnosed with cancer will survive at least 5 years,** according to a report published by the Centers for Disease Control and Prevention. The most common cancers continue to be prostate, female breast, lung and bronchus, and colon and rectum, the report noted. The full report, “Invasive Cancer Incidence and Survival—United States, 2011” is available at [www.cdc.gov/mmwr](http://www.cdc.gov/mmwr).

For more news on cancer research, visit *Cancer Discovery* online at <http://CDnews.aacrjournals.org>.